Characterization of the Adverse Effects Induced by Acetaminophen and Nonsteroidal Anti-Inflammatory Drugs Based on the Analysis of the Japanese Adverse Drug Event Report Database

Junko Nagai, BPharm, Yoshihiro Uesawa, PhD, Ryotaro Shimamura, BPharm, and Hajime Kagaya, PhD

Objectives: Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are antipyretic analgesics with established adverse effects (AEs); however, only a few studies have compared their AEs simultaneously. We aimed to compare the AEs of these medications to confirm the respective frequencies of both rare and major AEs.

Methods: We used a high-quality database for spontaneous adverse drug event reporting in Japan. Data were extracted regarding the AEs of acetaminophen and NSAIDs to compare the tendency of the appearance of those AEs between the drugs. We also performed a principal component analysis using the AE data to assess the characteristics of major AEs.

Results: Cutaneous disorders and hepatic disorders were the most common AEs induced by acetaminophen and NSAIDs, with gastrointestinal tract disorders also common with NSAID use. Principal component analysis quantitatively showed the tendencies of specific AEs, and it helped demonstrate the characteristics of AEs. Acetaminophen and NSAIDs showed different tendencies in the occurrence of AEs. Each NSAID was plotted based on the tendency of the appearance of major AEs, and AEs were classified by their likelihood of being pharmacological or idiosyncratic.

Conclusions: These findings may help clinicians select an appropriate drug for patients considering their backgrounds, instead of choosing merely based on the class of the drug, for example, cyclooxygenase selectivity. This selection, based on the characteristic information on AEs occurring in clinical settings, might be more suitable for patients.

Key Words: acetaminophen (paracetamol), nonsteroidal anti-inflammatory drugs, adverse effects, principal component analysis, Japanese Adverse Drug Event Report (JADER) database

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From the Department of Clinical Pharmaceutics, Meiji Pharmaceutical University, Tokyo, Japan.

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Reprints: Yoshihiro Uesawa, PhD, Department of Clinical Pharmaceutics, Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan (e-mail: uesawa@my-pharm.ac.jp).

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Acetaminophen (paracetamol) and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for symptoms of fever and pain and are frequently included in nonprescription forms available to the general public. Thus, these drugs are widely used worldwide. Although many patients undoubtedly receive benefit from them, some have experienced adverse drug reactions. Indeed, when selecting medical therapy, it is important to consider not only the desired therapeutic effects but also the possible adverse reactions, even for those medications that are temporarily used. Since the press release about the appropriate use of piroxicam[1] by the European Medicines Agency in 2007, it has been necessary to select the safest and most tolerable drug for each patient, especially when long-term use is required for chronic pain.

The phenomenon of population aging in Japan has led to sharp increases in the number of people with chronic pain, including the so-called "locomotive syndrome,"[2] cancer pain, and other diseases. However, given that there are 32 NSAIDs approved for use in Japan,[3] it can be difficult to select the most appropriate drug for each patient. Further information about the adverse effects (AEs) may help medical staff select drugs more rationally based on their characteristics, differences, and tendencies to cause adverse reactions.

AEs caused by acetaminophen and NSAIDs are well known because of their frequent use worldwide. Hepatic disorders are the most typical adverse drug reaction associated with acetaminophen and is a major cause of drug-related death in the United States. They have become a public health problem.[4] By contrast, the typical AEs induced by NSAIDs, as described in Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, include gastrointestinal tract disorder, kidney injury, hypersensitivity reaction,[5–11] and recently noticeable cardiovascular events.[12–15] There have been numerous studies conducted on these AEs, including experimental research about the selectivity to cyclooxygenase (COX) in each NSAID[16,17] and clinical research comparing some AEs between acetaminophen and several NSAIDs.[18–20] Thus, many studies and reports have been published regarding each drug and their main AEs. However, few clinical studies have sought to compare all AEs induced by acetaminophen and NSAIDs concurrently.

There are many methods of pharmacovigilance in place to protect patients and identify potential drug concerns. Indeed, there are many case reports of AEs that were not seen until the drug had been approved, either because they occurred rarely or because of the strict inclusion criteria of drug-development studies; a notable problem is that

patient characteristics in postmarketing settings frequently differ from those in clinical trials. This was shown in a recent pharmacoepidemiology study of adverse drug events performed using large-scale databases from medical institutions and insurance companies (claim data).[21] Spontaneous reporting databases also exist, such as the FDA Adverse Event Reporting System,[22] which are formed by regulatory agencies to facilitate postmarketing studies on drug AEs.[23,24] In Japan, the Japanese Adverse Drug Event Report (JADER) database is used for spontaneous AE reporting.[25]

The JADER database is a service offered by the Pharmaceuticals and Medical Devices Agency (PMDA) and has collected adverse drug event reports since it was established in April 2004. This database, which is open to the public through the Internet, provides updated information on a monthly basis and, as of October 2015, had amounted data for approximately 360,000 cases. The JADER database does not require data cleaning because it is provided as a complete database with more frequent reports and updates.[26] The JADER database contains data on reports using a format based on the E2B (M2) guideline of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

In this study, we examined the AEs induced by acetaminophen and NSAIDs as reported to the JADER database. We hoped that these findings obtained from data on the AEs of acetaminophen and each NSAID in Japan would provide helpful information when choosing a drug. To achieve this, we investigated the tendencies of these drugs to produce AEs and compared the AEs data. Using the JADER database ensured that this was informed by a large-scale accumulated database of patients in clinical settings.

MATERIALS AND METHODS

Study Design and Data Sources

This study was a database review of all AEs induced by acetaminophen and NSAIDs. The JADER database was downloaded from the PMDA Web site, and it included 365,729 reports of AEs recorded from April 1, 2004 to June 30, 2015.

TABLE 1. All 31 NSAIDs Approved for Use in Japan

Acemetacin	Mefenamic acid
Amfenac sodium hydrate	Meloxicam
Ampiroxicam	Mofezolac
Celecoxib	Nabumetone
Diclofenac sodium	Naproxen
Emorfazone	Oxaprozin
Epirizole	Piroxicam
Ethenzamide	Pranoprofen
Etodolac	Proglumetacin maleate
Flufenamate aluminum	Salicylamide
Flurbiprofen	Sodium salicylate
Ibuprofen	Sulindac
Indometacin	Tiaprofenic acid
Ketoprofen	Tiaramide hydrochloride
Lornoxicam	Zaltoprofen
Loxoprofen sodium hydrate	

NSAIDs indicates nonsteroidal anti-inflammatory drugs.

Definitions of Acetaminophen and NSAIDs

Acetaminophen was defined as any drug that included acetaminophen only but excluded any medications where acetaminophen was combined with other drug components. For the purpose of investigating the AEs of a single compound, we excluded fixed-dose combination drugs. For example, a combination drug of acetaminophen and tramadol is frequently prescribed in Japan. If this combination was included in the data on AEs of acetaminophen, AEs separate from those caused by tramadol, resulting from pharmacological effects of opioid μ receptor, such as constipation, nausea, and somnolence, would also be included.

We defined NSAIDs as those in the approved NSAID list downloaded from the Web site of the Ministry of Health, Labour and Welfare[3] (Table 1). Although acetylsalicylic acid (aspirin) is usually classified as an NSAID, its primary recorded use in the JADER database was for its antiplatelet effect, which is not seen with other NSAIDs; moreover, there were few reports of use for its anti-inflammatory effects (8.5%). Thus, the intended use of aspirin was clearly different from that of other NSAIDs; therefore, it was excluded from the NSAIDs list in this analysis. All remaining drugs in the NSAID list were merged and simply named "NSAIDs" for comparison with acetaminophen.

Removal of Duplicated Data

Case reports are presented in the JADER database in 4 tables: demographic, drug information, the adverse drug reaction and past medical history tables. As stated, any drugs in the NSAID list were merged and simply named NSAIDs in the drug information table. Then, we removed duplicated data from the drug information and adverse drug reaction tables using the methods described by Hirooka and colleagues.[27,28] Cases with the same identification number were merged in the adverse drug reaction, drug information, and demographic tables, thereby removing duplication.

Construction of Tables for Analysis

In each report, data for AEs from administered drugs were allocated to either suspected drug, coadministered drug, or drug interaction categories. We constructed tables for data analysis using only data for the suspected drug category and analyzed these data to assess the AEs induced by acetaminophen and NSAIDs. Next, two-by-two contingency tables were created to calculate the reporting odds ratios (RORs), structured by reports for the suspected drug, all other reports, reports with the suspected AEs, and reports without the suspected AEs (Table 2). The RORs, as used in pharmacovigilance to detect AEs signal, was calculated as $(a \times d)/(b \times c)$ with a two-by-two contingency table.[29] Calculation of the ROR and the associated 95% confidence intervals (CIs) as well as Fisher exact test were performed comprehensively for all combinations of drugs and AEs. Next, we created scatter plots to observe the tendency of the appearance of AEs by taking the natural logarithms of the RORs on the abscissa axis and the common logarithm of the inverse *P*-value (by Fisher exact test) on the vertical axis. Two-by-two contingency tables were built and analyzed in the same way for both NSAIDs and acetaminophen.

TABLE 2. Two-by-Two Contingency Table and Calculation Formula of ROR

	Reports With the Suspected Adverse Effect	Reports Without the Suspected Adverse Effect
Reports with the suspected drug	*a*	*b*
All other reports	*c*	*d*

ROR = $(a/c)/(b/d) = a \times d/b \times c$.

The contingency table is structured with reports for the suspected drug, all other reports, reports with the suspected adverse effects, and reports without the suspected adverse effects (a-d indicate the numbers of reports). The ROR was calculated as shown.

ROR indicates reporting odds ratio.

Principal Component Analysis (PCA)

PCA was performed using the tendency of typical AEs induced by acetaminophen and NSAIDs as the characteristic data for each drug. As major AEs, we choose from the more frequent items in the initial analysis. In addition, we included AEs detailed as warnings or contraindications on drug package inserts of acetaminophen and NSAIDs. The information provided on these package inserts often dictates the behavior of medical staff because of its use in judicial decisions pertaining to medicolegal actions in Japan.[30] Thus, we selected 7 AEs caused by acetaminophen and NSAIDs as "major AEs." These AEs are generally considered to lead to severe outcomes and are clinically important.

These were labeled according to the Standardized MedDRA Queries[31] of the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J) (version 18.0) because it records AEs using preferred terms from the MedDRA/J[32] in the JADER database, and it uses only a narrow region. Preferred terms for gastrointestinal tract disorders related to embolism were excluded. Seven kinds of major AEs were identified and are shown in Table 3.

The next step was to analyze each major AE to find data that characterized the AEs of these drugs for application to PCA. This process was performed using the generic name of each NSAID in the drug information table from the JADER database.

Again, duplicate data were removed using the method described by Hirooka, and the data table was merged using each case number. We only extracted the data for cases where the indicated drug was listed as the primary suspected drug and oral formulations from the JADER database for the analysis. Some NSAIDs were available in nonoral formulations, including patches, suppositories, and injections. Because these formulations cause route-specific AEs, the AE distribution could alter among NSAIDs not marketed in these formulations.

Again, two-by-two contingency tables were created, and the RORs were calculated. We performed PCA using the natural logarithms of the RORs for each major AE of acetaminophen and each drug in the NSAID list.

Statistical Analysis

All data analyses were performed using JMP Pro 12.1.0 (SAS Institute Inc., Cary, NC). If a two-by-two contingency table contained zero in a cell, the ROR was not calculable, and the estimate was considered to be unstable if the number was too small. Therefore, we performed Haldane-Anscombe 1/2 corrections (ie, the addition of 0.5 to all cells) to correct this bias.[33] Any P-value < 0.05 was considered significant.

TABLE 3. Seven Major Adverse Effects and SMQ Code

Adverse Effect	SMQ Code	SMQ
Acute renal failure	20000003	Acute renal failure (SMQ)
Asthma/bronchospasm	20000025	Asthma/bronchospasm (SMQ)
Drug-related hepatic disorders—comprehensive search	20000009	Cholestasis and jaundice of hepatic origin (SMQ)
	20000013	Hepatic failure, fibrosis, and cirrhosis and other liver damage–related conditions (SMQ)
	20000010	Hepatitis, noninfectious (SMQ)
	20000012	Liver neoplasms, benign (including cysts and polyps) (SMQ)
	20000208	Liver malignant tumors (SMQ)
	20000209	Liver tumors of unspecified malignancy (SMQ)
	20000008	Liver-related investigations, signs, and symptoms (SMQ)
	20000015	Liver-related coagulation and bleeding disturbances (SMQ)
Embolic and thrombotic events	20000082	Embolic and thrombotic events, arterial (SMQ)
	20000084	Embolic and thrombotic events, venous (SMQ)
	20000083	Embolic and thrombotic events, vessel type unspecified, and mixed arterial and venous (SMQ)
Gastrointestinal perforation, ulceration, or hemorrhage	20000108	Gastrointestinal hemorrhage (SMQ)
	20000107	Gastrointestinal perforation (SMQ)
	20000104	Gastrointestinal perforation, ulcer, hemorrhage, obstruction nonspecific findings/procedures (SMQ)
	20000106	Gastrointestinal ulceration (SMQ)
Severe cutaneous adverse reactions	20000020	Severe cutaneous adverse reactions (SMQ)
Tubulointerstitial diseases	20000221	Tubulointerstitial diseases (SMQ)

SMQ indicates Standardized MedDRA Queries.

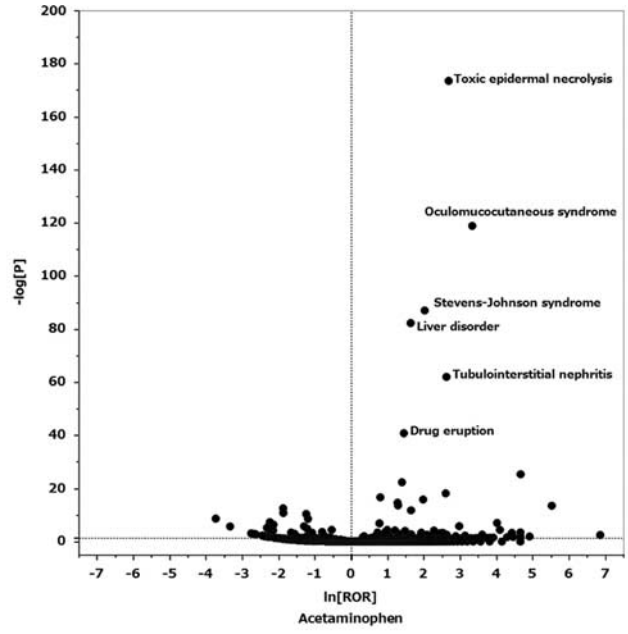
RESULTS

Adverse Effects Induced by Acetaminophen and NSAIDs

Figures 1 and 2 show the AEs of acetaminophen and NSAIDs, respectively. Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome, and Stevens-Johnson syndrome (SJS) were plotted in the upper right area

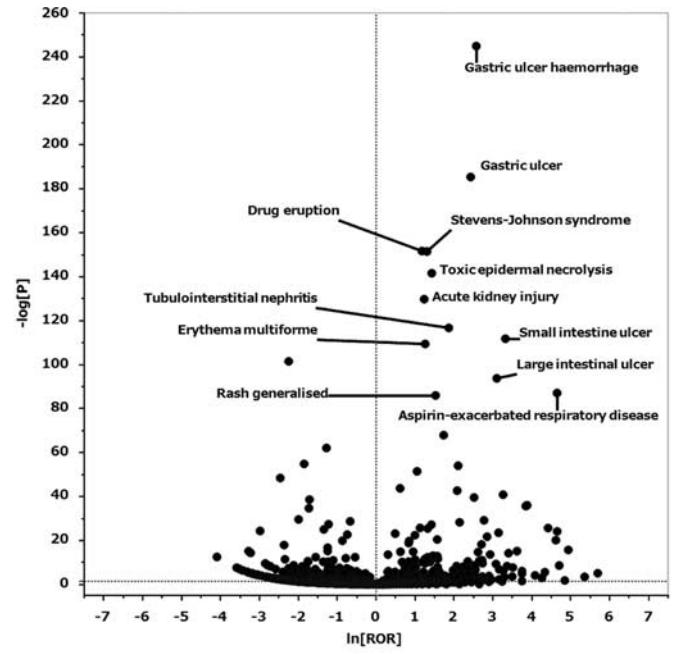
in Figure 1. These AEs were classified as severe cutaneous AEs. Therefore, these results indicate that severe cutaneous AEs are characteristic AEs of acetaminophen. In Figure 2, gastric ulcer hemorrhage and gastric ulcer were plotted in the upper right area. It shows that gastrointestinal ulceration is a characteristic AE of NSAIDs.

From aggregate results of reports for acetaminophen, TEN was the most reported AE (n = 233), with an ROR of 14.69 (95% CI, 12.82-16.83), followed by liver disorder (n = 232; ROR = 5.16; 95% CI, 4.51-5.91). Most AEs were classified as either hepatic disorders or cutaneous disorders (79.0%). For the NSAIDs group, drug eruption was the most reported AE (n = 739; ROR = 3.28; 95% CI, 3.04-3.54), and similar to acetaminophen, most AE were classified as either hepatic disorders or cutaneous disorders. In addition, NSAIDs were associated with gastrointestinal tract AEs, among which gastric ulcer hemorrhage was the most frequent (n = 365; ROR = 13.24; 95% CI, 11.77-



adverse event	ROR	95% confidence interval	P value	n	Reporting ratio (%)
Toxic epidermal necrolysis	14.69	(12.82-16.83)	<0.0001	233	7.93
Liver disorder	5.16	(4.51-5.91)	<0.0001	232	7.89
Stevens-Johnson syndrome	7.60	(6.51-8.87)	<0.0001	175	5.95
Hepatic function abnormal	2.24	(1.89-2.64)	<0.0001	148	5.03
Drug eruption	4.28	(3.60-5.09)	<0.0001	136	4.63
Oculomucocutaneous syndrome	28.13	(23.22-34.09)	<0.0001	117	3.98
Tubulointerstitial nephritis	13.83	(11.09-17.24)	<0.0001	84	2.86
Erythema multiforme	4.06	(3.24-5.09)	<0.0001	77	2.62
Pyrexia	1.43	(1.11-1.84)	0.0094	62	2.11
Rash	2.18	(1.69-2.83)	<0.0001	59	2.01
Anaphylactic shock	1.39	(1.07-1.80)	0.0199	58	1.97
Drug reaction with eosinophilia and systemic symptoms	3.60	(2.77-4.68)	<0.0001	57	1.94
Drug-induced liver injury	3.64	(2.77-4.79)	<0.0001	52	1.77
Acute kidney injury	1.44	(1.03-2.00)	0.0433	35	1.19
Abnormal behaviour	7.27	(5.10-10.37)	<0.0001	31	1.05

FIGURE 1. Most frequently reported adverse effects induced by acetaminophen. The abscissa of the scatter plot is a natural logarithm of the ROR (lnROR) axis. The ordinate of the scatter plot is a common logarithm of inverse *P*-values (−log *P)* by Fisher exact test axis; a *P*-value of 0.05 is shown by the dotted line of ordinate. As ROR becomes more positive, there is a greater tendency of adverse effects, and decreasing *P*-values indicate that these are more statistically significant. Accordingly, adverse effects plotted to the top and right of the scatter plot suggest the effect is significantly characteristic. Adverse effects are listed in order of frequency and ranked for the top 15. n is the number of reports. Reporting ratio (%) is a ratio of a number of 1 "adverse effect" report and all reports of acetaminophen. ROR indicates reporting odds ratio.



adverse event	ROR	95% confidence interval	P value	n	Reporting ratio (%)
Drug eruption	3.28	(3.04-3.54)	<0.0001	739	3.46
Hepatic function abnormal	1.37	(1.27-1.48)	<0.0001	671	3.14
Liver disorder	1.87	(1.72-2.03)	<0.0001	639	2.99
Stevens-Johnson syndrome	3.73	(3.44-4.06)	<0.0001	621	2.91
Acute kidney injury	3.47	(3.19-3.78)	<0.0001	582	2.72
Toxic epidermal necrolysis	4.22	(3.85-4.63)	<0.0001	501	2.34
Anaphylactic shock	1.65	(1.50-1.80)	<0.0001	496	2.32
Erythema multiforme	3.56	(3.24-3.91)	<0.0001	473	2.21
Gastric ulcer haemorrhage	13.24	(11.77-14.90)	<0.0001	365	1.71
Gastric ulcer	11.45	(10.08-13.02)	<0.0001	298	1.39
Drug-induced liver injury	2.89	(2.57-3.26)	<0.0001	294	1.38
Tubulointerstitial nephritis	6.54	(5.75-7.43)	<0.0001	272	1.27
Rash generalised	4.66	(4.11-5.28)	<0.0001	271	1.27
Rash	1.36	(1.20-1.53)	<0.0001	269	1.26
Renal impairment	1.38	(1.22-1.57)	<0.0001	257	1.20

FIGURE 2. Most frequently reported adverse effects induced by NSAIDs. The abscissa, ordinate, and interpretation of the scatter plot are the same as reported in Figure 1. Thus, adverse effects plotted to the top and right of the scatter plot suggest that the effect is significantly characteristic. Adverse effects are listed in order of frequency and ranked for the top 15. n is the number of reports. Reporting ratio (%) is the ratio of the number of 1 "adverse effect" report to all reports in NSAIDs. NSAIDs indicates nonsteroidal anti-inflammatory drugs; ROR, reporting odds ratio.

14.90). Interestingly, this was also present to a lesser degree for acetaminophen (n = 5; ROR = 1.1; 95% CI, 0.4-2.6). Acute renal injury caused by NSAIDs was also more frequent (n = 232) and had a higher ROR than acetaminophen (ROR = 3.47; 95% CI, 3.19-3.78).

Characterization of Adverse Effects by PCA

Data on the primary suspected drug and oral administration were extracted from the JADER database and corresponded to 27 drugs in the NSAID list (Table 1). There were no adverse drug reactions induced by emorfazone or salicylamide in the JADER database. Moreover, data on adverse drug reactions induced by ethenzamide or sodium salicylate did not satisfy the extraction criteria. Therefore, we performed PCA using 28 drugs that contained acetaminophen and 27 NSAIDs that excluded these 4 drugs from the NSAID list.

Acetaminophen was plotted in a negative region on the axis of the first principal component and a positive

region on the axis of the second principal component, far from the NSAIDs. Celecoxib, meloxicam, and etodolac, each of which has high selectivity for COX-2, were plotted in a negative direction on both the first and second principal component axes.

All loading vectors show that the 7 major AEs were positive in direction for the first principal component. Severe cutaneous adverse reactions, drug-related hepatic disorders, and tubulointerstitial disease each sloped up in a positive direction for the second principal component. Acute renal failure, embolic and thrombotic events, gastrointestinal perforation ulceration, and hemorrhage each sloped down in a negative direction for the second principal component.

DISCUSSION

Adverse Effects Caused by Acetaminophen and NSAIDs

Severe cutaneous reactions and drug-related hepatic disorders were the most commonly seen AEs for both acetaminophen and NSAIDs. An epidemiological study on SJS and TEN from 2005 to 2007 in Japan reported that antipyretic analgesics were the most suspected drug class.[34] Thus, when acetaminophen or NSAIDs are administered, health care providers should consider the possibility of these AEs and explain the risk, countermeasures, and need to remain vigilant. By contrast, hepatic disorders are known to occur in a dose-dependent manner with acetaminophen.[35] We tried to examine the effect of dosage in this study but could not obtain correct dosage information because of limitations with the JADER database. To provide a reference, we therefore calculated the estimated daily dose, approximately 10% of all cases reported acetaminophen use at doses over 1500 mg per day, and only a few cases exceeded 4000 mg per day.

Overall, although case reports of drug-related hepatic disorders induced by high-dose acetaminophen are becoming a health care problem in the United States, there are still only a few cases in Japan. This is interesting because the approved dose of acetaminophen was raised to 4000 mg per day in 2011 in Japan, and it has become easy to administer higher doses. The research that led to this change reported that the risk of hepatic disorders by high-dose administration of acetaminophen was comparable between Japanese and other races.[36] Moreover, there are now more options for the route of administration, although acetaminophen is generally not the preferred drug for pain treatment because the previously approved dosage of 1500 mg was insufficient to produce analgesia. Nevertheless, changes in the availability and approved dosage may increase the number of patients using acetaminophen and the doses taken when compared with the past.[37,38] Considering the possibility that patients were excluded from the research—for example, because they were considered high risk for unintended overdose through duplicate use with prescription drugs and nonprescription drugs that include acetaminophen—it will be necessary to watch carefully for the trend in usage and AEs in Japan in the future.

Gastrointestinal tract disorders were reported most frequently in the analysis of AEs for NSAIDs. This is consistent with knowledge that NSAIDs have a risk of gastrointestinal tract disorders that increases with their potency of COX-1 inhibition.[39] In comparison with NSAIDs, there were few reports of gastrointestinal tract disorders associated with acetaminophen, and the ROR was small. These results are consistent with recommendations that nonprescription oral formulations of acetaminophen can be taken in the fasting state, unlike

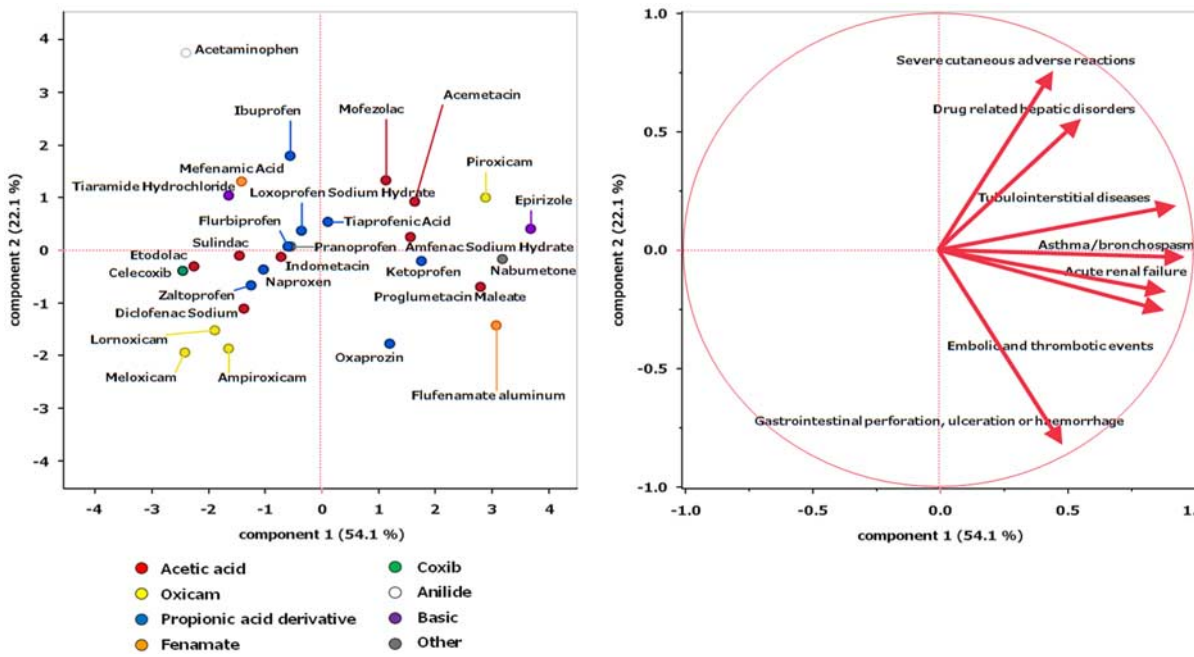


FIGURE 3. Results of the principal component analysis of adverse effects for acetaminophen and NSAIDs. The score plot is depicted for the principal component analysis of adverse effect data for acetaminophen and NSAIDs. Each loading vector indicates a major adverse effect, and each dot indicates each drug. The dots are colored based on their chemical classification. NSAIDs indicate nonsteroidal anti-inflammatory drugs.

NSAIDs, and with the hypothesis that acetaminophen has a weak effect on COX inhibition in the periphery.[40] Nevertheless, the pharmacological mechanism of acetaminophen remains unclear, and several cases of gastrointestinal tract disorders were reportedly induced by acetaminophen. To use acetaminophen with more safety, we must better understand the underlying causative mechanism and the role of patient characteristics.

Characterization of Adverse Effects Caused by Each Drug Using PCA

PCA of the AE data for acetaminophen and NSAIDs is summarized in Figure 3. All loading vectors with AEs were positive for the first principal component, indicating that acetaminophen and NSAIDs are likely to cause the major AEs when compared with other drugs extracted from the JADER database. NSAIDs with positive values in the first components included various type of chemical classifications. The number of case reports for these drugs was < 10, and it was considered that there was probably little consumption of these drugs in Japan compared with other NSAIDs. These drugs had RORs that were greater than other drugs and corresponded mostly to major AEs.

AEs that pointed in a positive direction in the second principal component were severe cutaneous adverse reactions, drug-related hepatic disorders, and tubulointerstitial disease. Severe cutaneous adverse reactions and drug-related hepatic disorders include idiosyncratic AEs that appear despite correct dosage and administration for some patients.[41]

In the second principal component, gastrointestinal tract disorders, embolic and thrombotic events, and acute renal failure were negatively directed. We considered that these AEs were caused by the potency of COX inhibition rather than the constitution of patients. It is also known that hypersensitivity to NSAIDs, as represented by aspirin-induced asthma, is caused by the inhibition of COX-1.[42,43] Therefore, the second principal component axis likely showed the mechanism of AEs, making it possible to understand the classification of AE relative to each drug.

The wide variety of drugs causing AEs can be classified into types A, B, or C based on their mechanism.[44,45] The positive direction in the second principal component in this PCA indicated the tendency of AEs to appear according to both the pharmacological effect of each drug and the constitution of each patient (ie, type B or C AEs). By contrast, the negative direction in the second principal component indicated the tendency of AEs to be due to the pharmacological effect of each drug (ie, type A AE). Asthma and bronchospasm are caused by both pharmacological effects and patients' constitutions; therefore, this loading vector overlapped an axis of the second principal component. Some published reviews have applied the AEs of NSAIDs to type A and B,[42] illustrating cardiovascular events and gastrointestinal tract disorders as effects of 6 NSAIDs.[46] This offers a rough classification limited to the risk of hypersensitivity for each NSAIDs,[43] although there has been only limited information for individual drugs about multiple AEs.

We also showed the tendencies and likely occurrence of 7 major AEs induced by acetaminophen and NSAIDs. Using PCA, each drug's positional relationship can be understood relative to the characteristic AEs they induce. These positional relationships suggest that neither drug induces major AEs in the NSAIDs group and that any effects result from a mechanism that combines COX inhibition and patients' constitutions.

Acetaminophen was plotted far from the NSAIDs, consistent with it showing characteristic AEs that are different from those of NSAIDs. Major AEs with acetaminophen were probably less due to COX inhibition and more due to constitutional issues. The configurations of each drug in the score plot by PCA were not necessarily consistent with classification by chemical structure or selectively for COX-1 and COX-2, suggesting that some unknown pharmacological mechanism may be involved in these AEs.

Drug selection in clinical settings is usually based on recommendations from disease-specific guidelines, which in turn are based on known facts on treatment and the AEs of each drug. Usually, the selection of antipyretic analgesic in Japan is done according to the class of the drug (ie, COX selectivity and acidicity). Furthermore, drug selection seeks to avoid AEs, whereas other drugs may be selected to prevent AEs. The JADER database includes data on AE reports caused by drugs selected for patients in clinical settings. Thus, it does not simply estimate the possibility of the occurrence of AE. In this study, results of the PCA using the JADER database provided information about the characteristics and tendency of AEs induced by acetaminophen and NSAIDs in Japan. They clearly indicate the relationships of the characteristics of AEs caused by each drug in addition to drug classification information. These findings might help with rational drug selection based on patient backgrounds.

Limitations

Our study has several limitations. It is known that studies using spontaneous AE reporting databases are associated with various biases.[47,48] SJS and TEN are rare but severe adverse drug reactions that require hospitalization for urgent treatment. Thus, reporting bias is possible because these are reported more frequently than mild or well-known AEs.[49] Another limitation is that causal relationships between drugs and AEs in the JADER database are only verified by the PMDA for fatalities, with other outcomes only estimated by the reporter; consequently, we cannot be certain that all AEs were caused by the medications listed. We were also unable to use patient characteristics to assess the risk of appearance of AEs, including genetic polymorphisms and clinical laboratory test results, because these are not included in the JADER database. However, we anticipate that these problems can be remedied by combining information about drug properties with research into their specific AEs in various patient populations.

CONCLUSIONS

Acetaminophen and NSAIDs are widely used worldwide and are also known to cause important AEs. Drug selection, even with these common medications, should consider their characteristic AEs and the backgrounds of patients such as age, organ functions, concomitant drugs, and past medical histories. Currently, antipyretic analgesics tend to be selected from among acetaminophen, selective COX-2 inhibitors, and nonselective NSAIDs. In this study, we were able to classify the characteristics and tendencies of AEs induced based on these classes in Japan. These findings may offer invaluable reference information when selecting antipyretic analgesics based on the risk of AEs.

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